

WHAT IS CLAIMED IS:

1. A method of identifying a secondary target site comprising:

(a) providing a plurality of cells having a genome, which includes at least one primary gene encoding telomerase activity and a promoter that can direct the over expression of said primary gene;

(b) effecting one or more mutations in the genome of said cells, at one or more secondary sites;

(c) selecting those cells having at least one mutation that proves lethal to said cells when said primary gene is over expressed;

(d) determining a site in the genome of said cells in which said at least one lethal mutation is located, to provide a secondary target site.

2. The method of claim 1 in which said secondary target site includes a *tol* gene, a homolog thereof, or an analog thereof, including mammalian homologs or analogs thereof.

3. The method of claim 2 in which said *tol* gene is selected from the group consisting of *toll*, *tol2*, *tol3*, a homolog thereof, or an analog thereof, including mammalian homologs or analogs thereof.

4. The method of claim 1 in which said secondary target site or any gene product thereof is involved in either the modulation of the expression of said primary gene or a process affecting the viability of the cell in which said primary gene is over expressed.

5. The method of claim 1 in which said at least one primary gene is selected from the group consisting of *EST1*, *EST2*, *EST3*, *TLC1*, a homolog thereof, an analog thereof, including mammalian homologs or analogs thereof, or combinations thereof.

6. The method of claim 2 in which a homolog or an analog of said *tol* gene is selected from the group consisting of *CHL1*, a gene encoding human helicase, *ercc2*, a gene encoding mouse DNA helicase, or a gene encoding human type II keratin subunit protein.

7. The method of claim 5 in which said *TLC1* gene is selected from the group consisting of *embZ35904*, *gbU14595*, *embZ35905*, *dbjD28120*, *gbL24113*, *embX76992*, *gbAC005476.3*, *gbU53340*, including mammalian homologs or analogs thereof, or combinations thereof.

8. The method of claim 5 in which said *EST1*, *EST2*, and *EST3* genes are selected from those genes encoding human kininogen HMW heavy chain, prepro alpha-2-thiol proteinase, calmodulin-stimulated protein, kininogen, immunoglobulin kappa chain, nitric-oxide synthase, immunoglobulin heavy chain variable, T-cell receptor delta-chain V, Ig gamma-chain, Ig H-chain V-D-JH4-region, perlecan, insulin-like growth factor II, interferon-alpha, rat coding sequence of p15 and p12, interferon-alpha I precursor, AAD10, or combinations thereof.

9. The method of claim 1 which further comprises using said secondary target site, or lethal mutations thereof, to screen for a drug or drug candidate.

10. The method of claim 9 in which said drug or drug candidate inhibits the growth or replication of a human tumor or causes the demise of said human tumor.

11. The method of claim 9 in which said drug or drug candidate interacts with, binds to, or inhibits the expression or activity of a gene product associated with said secondary target site.

12. The method of claim 9 in which said drug or drug candidate comprises a polypeptide, an oligonucleotide, a polysaccharide, or a small molecule.

13. A secondary target site comprising a site in the genome of a cell, which genome includes at least one primary gene encoding telomerase activity and a promoter that can direct the over expression of said primary gene, said site able to accommodate at least one mutation that can prove lethal to said cell when said primary gene is over expressed.

14. The lethal mutations of the secondary target site of claim 13 and allelic variations thereof.

15. A method of inhibiting the growth or replication of a tumor cell or causing the demise of said cell, said cell exhibiting aberrant telomerase activity, comprising administering a drug or drug candidate that interacts with, binds to, or inhibits the expression or activity of a gene product associated with a secondary target site in the genome of said cell, which site can accommodate at least one mutation that can prove lethal to said cell.

16. The method of claim 15 in which a secondary target site includes a tol gene, a homolog thereof or an analog thereof, including mammalian homologs or analogs thereof.

17. The method of claim 15 in which said tol gene is selected from the group consisting of tol1, tol2, tol3, a homolog thereof, or an analog thereof, including mammalian homologs or analogs thereof.

18. The method of claim 15 in which said aberrant telomerase activity comprises overexpression of telomerase.

19. A pharmaceutical composition comprising an effective amount of a drug or drug candidate and a pharmaceutically acceptable carrier or diluent, said drug or drug

candidate capable of interacting with, binding to, or inhibiting the expression or activity of a gene product associated with a secondary target site in the genome of a cell exhibiting aberrant telomerase activity, which site can accommodate at least one mutation that can prove lethal to said cell.

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20. A pharmaceutical composition of claim 19 in which said aberrant telomerase activity comprises overexpression of telomerase.

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21. A recombinant eukaryotic cell comprising at least one secondary target site, a homolog thereof, or an analog thereof and at least one primary gene, a homolog thereof, or an analog thereof, wherein said at least one primary gene encodes telomerase and said at least one secondary target site contains a mutation such that the up regulation, down regulation, elimination, or disruption of said at least one primary gene gives rise to senescence or synthetic lethality.

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22. A method of screening for drugs, comprising:

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(a) providing one or more eukaryotic cells capable of telomerase overexpression, which one or more cells exhibit senescence or synthetic lethality under conditions of telomerase overexpression when a wild-type tol gene, its homolog, or its gene product of said one or more cells is mutated;

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(b) contacting said one or more cells with one or more drug candidates under conditions that provide telomerase overexpression and, optionally, inhibition or mutation of said wild-type tol gene, its homolog, or its gene product; and

(c) selecting those drug candidates that give rise to senescence or synthetic lethality under conditions that provide telomerase overexpression or those drug candidates that inhibit, suppress, reverse, or prevent senescence or

23. A secondary target site identified by the method of claim 1.

24. A method of inhibiting the growth or replication of a tumor cell or causing  
 25. death of said cell, said cell exhibiting aberrant telomerase activity, comprising  
 26. administering a drug or drug candidate that interacts with, binds to, or inhibits (or  
 27. reduces) the expression or activity of a gene product associated with the secondary  
 28. site of claim 21.

25. A pharmaceutical composition comprising an effective amount of a drug or drug candidate and a pharmaceutically acceptable carrier or diluent, said drug or drug candidate capable of interacting with, binding to, or inhibiting (or enhancing) the expression or activity of a gene product associated with the secondary target site of claim 21.

26. The pharmaceutical composition of claim 25 in which said secondary target site is found in the genome of a cell exhibiting aberrant telomerase activity.

27. The pharmaceutical composition of claim 25 in which said aberrant telomerase activity comprises overexpression of telomerase.

28. A method of inhibiting the growth or replication of a tumor cell or causing the demise of said cell, said cell exhibiting aberrant telomerase activity, comprising administering a drug or drug candidate that interacts with, binds to, or inhibits (or enhances) the expression or activity of a gene product associated with a secondary target site.

29. A pharmaceutical composition comprising an effective amount of a drug or drug candidate and a pharmaceutically acceptable carrier or diluent, said drug or drug

candidate capable of interacting with, binding to, or inhibiting the expression or activity of a gene product associated with a secondary target site in the genome of a cell exhibiting aberrant telomerase activity.

- 5           30.   The pharmaceutical composition of claim 29 in which said aberrant telomerase activity comprises overexpression of telomerase.

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